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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/720,066	10/19/2001	Michael Hallek	50125/019001	8894

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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

DATE MAILED: 12/15/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/720,066	HALLEK ET AL.	
	Examiner	Art Unit	
	Maria B. Marvich, PhD	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/2/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,31,32,35-42 and 44-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,31, 32, 35-42 and 44-52* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 November 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/2/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/2/06 has been entered.

Claim Objections

Claims 1, 41, 42 and 51 are objected to because of the following informalities: Applicants refer alternatively to AAV, AAV2, adeno-associated virus 2 and adeno-associated virus throughout the claims. For clarity it would be remedial to indicate on the first occurrence of the phrase adeno-associated virus in claim 1 that it is abbreviated AAV for example -- adeno-associated virus (AAV) -- and -- adeno-associated virus 2 (AAV2) --. Thereafter, applicants can reference adeno-associated virus by its abbreviation.

In claims 41 and 51, applicants recite "the method" in line 2. However, the claims actually recite "A process". While it is clear that applicants intend to reference the process by recitation of "the method", it would be more accurate to recite -- the process--.

Claim 42 recites "an AAV2 coding for a mutated structural protein of". The phrase is incomplete for two reasons, first the genome or a nucleic acid of AAV2 encodes the structural protein and reference to AAV customarily indicates the particle, for accuracy, it would be remedial to indicate that it is the nucleic acid of AAV2 encoding the mutated structural protein.

Secondly, the phrase lacks an object of the preposition "of". It would be remedial to complete the phrase. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 31, 32, 35-42, 45, 49, 50 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 35, 39, 45, 49 and 52 are vague and indefinite in that the metes and bounds of "the one or more (amino acid) insertions" are unclear. The dependent claims are included in the rejection because they fail to address or clarify the basis of the rejection as discussed in detail for the independent claims. Claims 1, 31, 32, 35-40, 45, 49, 50 and 52 are drawn to a structural protein with one or more insertions located directly adjacent and after the N in SEQ ID NO:7. As there is only one site located immediately adjacent and after any amino acid, it is unclear how the site immediately adjacent and after amino acid N in SEQ ID NO:7 can have more than one insertion. While a single insertion can comprise more than one amino acid, the recitation of "one or more insertions" or "one or more amino acid insertions" is drawn to a number events in which amino acids are inserted into the structural protein. **This is a new rejection necessitated by applicants' amendment.**

Claim 1, 31, 39 and 41 are vague and indefinite in that the metes and bounds of "which brings about an increase in the infectivity of AAV" are unclear. The dependent claims are

included in the rejection because they fail to address or clarify the basis of the rejection as discussed in detail for the independent claims. The claims recite an isolated structural protein comprising amino acid insertions, which bring about an increase in infectivity of the AAV. Because the claims do not set forth the relationship between the AAV and the structural protein, it is unclear if the increase in infectivity is brought about when the mutated structural protein is a part of the AAV or if the isolated structural protein independent of AAV causes an effect on AAV infectivity. In the later situation, this can be envisioned for example if the protein is administered to cells and competes for secondary receptors. **This is a new rejection.**

The term "change" in claim 31 is a relative term, which renders the claim indefinite. The term "change" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. It is unclear to what the interaction parameters of the protein are compared. **This is a new rejection.**

Claim 31 is vague and indefinite in that the metes and bounds of "the mutation" are unclear. The claims are drawn to a structural protein that comprises at least one mutation. Therefore, it is unclear if by recitation of "the mutation" in claim 31, if applicants intend one of the mutations or all of the mutations. **This is a new rejection.**

Claim 40 is vague and indefinite in that the metes and bounds of "a nucleic acid according to claim 39" are unclear. By recitation of "a nucleic acid", it is unclear if any nucleic acid of claim 39 or if the entire nucleic acid of claim 39 is required in the isolated cell of claim 40. if it is the later, it would be remedial to recite -- the nucleic acid of claim 39 --. **This is a new rejection.**

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41 and 42 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants claim a process of producing a mutated structural protein of AAV2 and a method of using the mutated structural protein of AAV2 in which the mutated structural protein comprises a genus of structural proteins comprising at least one mutation, wherein the mutated structural protein comprises one or more amino acid insertion, which brings about an increase in infectivity of AAV (claims 41 and 42). The amino acid insertions are located before and/or after at least one amino acid sequence found in SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8, wherein the mutated structural protein is capable of particle formation. **This is a new rejection.**

The written description requirement for genus claims may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with known or disclosed

correlations between function and structure, or by a combination of such characteristics sufficient to show that the applicant was in possession of the claimed genus.

Although the instant claims are directed to methods, adequate description of the methods first requires an adequate description of the materials, which provide the means for practicing the invention. The Guidelines for Written Description state "The claimed invention as a whole may not be adequately described if the claims require an essential or critical element which is not adequately described in the specification and which is not conventional in the art". The instant invention recites a process of producing a mutated structural protein of AAV2 and methods of using the mutated structural protein of AAV2 in which the mutated structural protein comprises at least one mutation wherein the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. The amino acid insertion is directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. These sequences are found in AAV2 capsid proteins (see page 17, line 8-23). Furthermore, the claims are drawn to a nucleic acid coding for these structural protein as well as cells comprising the nucleic acid. As well, the claims are drawn to methods of preparing the structural proteins and use of the structural proteins to alter tropism of AAV2. The critical element of all of the claims is a structural protein comprising a mutation with one or more amino acid insertions.

The specification defines "structural proteins " as capsid proteins, which are VP1, VP2 and VP3 (see page 1, paragraph 2 and 3). These proteins are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see page 2, line 1-10). The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop

structures that were identified within the capsid proteins VP1, VP2 and VP3 of AAV2 (see page 11, line 10-18). These regions were identified by comparison of the crystal structure and nucleic acid sequences of three viruses CPV, AAV2 and B19. By insertions of amino acids within the loops, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

The potential mutations are large in number and diverse for the following reasons. By recitation of "amino acid insertion(s)", the insertion can be as small as a single amino acid or as large as a gene. Secondly, there can be multiple insertions within the structural protein, which leads to a complex and large number of possible structural proteins. For example, considering a single insertion prior to or after the recited amino acids, a collection of proteins would be generated totaling about 77. This collection would increase exponentially upon introduction of multiple mutations within the singly mutated proteins. As guidance, applicants have only demonstrated insertion of a laminin P1 ligand into VP1 and VP3 (pages 16-20). Specifically, Tables 1 and 2 depict five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (ins447 or I-447), directly following FF in SEQ ID NO:5 (ins534 or I-534), directly following T in SEQ ID NO: 6 (ins573 or I-573), directly following N in SEQ ID NO:7 (ins587 or I-587) and directly following T in SEQ ID NO:8 (ins713 or I-713). One viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of M07-LP1-R and B16F10 cells. Therefore, of these insertions, only one can tolerate the mutation and form particles and have increased infectivity. This mutation is at site 587 (I-587). The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein

to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol. 76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3.

The disclosure of insertion of the P1 ligand at amino acid 587 of VP3 to alter specificity to the two cell types is not accompanied by a disclosure as to the relative properties of this structural protein or a correlation between the structure of this mutation and its ability to alter infectivity. Therefore, following the guidance in the specification only a single site of insertion has been identified and that is after amino acid 587 of AAV2 VP3. Hence, there is no clear description of the structural or functional characteristics required for any other mutated structural proteins to increase infectivity. Given the large number of mutant structural proteins envisioned by the invention and the inability to determine which mutant structural proteins will increase infectivity and be capable of particle formation, it is concluded that the invention must be empirically determined. In an unpredictable art, the disclosure of a single species would not represent to the skilled artisan a representative number of species sufficient to show applicants were in possession of claimed genus. Therefore, the skilled artisan cannot envision the detailed structure of the broad class of recited AAV mutant structural proteins regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that the protein is part of the invention and a reference to a potential method for isolating it. The disclosure of a single member of this genus does not suggest that the applicant was in possession of the genus.

Claim Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 41, 42, 44, 46-48, 50 and 51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a structural protein of AAV2 which comprises a single amino acid insertion immediately following amino acid N in SEQ ID NO:7 (amino acid 587 of AAV2 VP3), does not reasonably provide enablement for any other structural protein of AAV2 which comprises amino acid insertion(s) is (are) directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. **This is a new rejection necessitated by applicants' amendment except in the case of claims 41 and 42 where this is a new rejection.**

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.*, 8 USPQ2d 1217 (Fed. Cir. 1988)). Whether undue experimentation is required is not based on a single factor but is rather a conclusion reached by weighing many factors (See *Ex parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Inter, 1986) and In *re Wands*, 8USPQ2d 1400 (Fed. Cir. 1988); these factors include the following:

1) **Nature of invention**. Applicants claim a process of producing a mutated structural protein of AAV2 (claim 41) and methods of using the mutated structural protein of AAV2 (claim 42) and mutated structural proteins (claims 44, 46-48, 50 and 51) in which the mutated structural protein comprises a genus of structural proteins comprising at least one mutation. In claims 41 and 42, the mutated structural protein comprises one or more amino acid mutations that bring about an increase in infectivity. The structural protein is also capable of particle formation. In these claims, applicants endeavor to modify the capsid proteins such that they are more specific and efficient gene transfer vectors (see e.g. page 5, paragraph 3).

2) **Scope of the invention.** The amino acid insertions are directly adjacent to at least one amino acid in the sequences listed as SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8. The recited sequences within SEQ ID NO: 2, 3, 4, 5, 6, 7 and 8 represent loop structures that were identified within the capsid proteins VP1, VP2 and VP3 by comparison of the crystal structure as well as the nucleic acid sequences of three viruses CPV, AAV2 and B19 (see page 11, line 10-18). Given the broad range of points of insertion, the undefined nature of the requisite number of insertions and number of amino acids that comprise the insertion, the claims encompasses broad and diverse collection of structural proteins. The insertion is intended to be of amino acids that function to increase infectivity. It would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV that is capable of particle formation and can alter tropism of AAV2. In the case of claims 44, 46-48, 50 and 51, the claims have been expanded to include embodiments that are inoperative for the only use that are disclosed in the specification, an increase in infectivity of AAV of an AAV that is capable of particle formation

with altered tropism. Applicants have not disclosed an enabled use for the mutated structural protein of claims 44, 46-48, 50 and 51.

3) **Number of working examples and guidance**. VP1, VP2 and VP3 are encoded by overlapping sequences of the same open reading frame leading to obligatory expression of all the capsid proteins (see e.g. page 2, line 1-10). Following identification of "loop structures", applicants, as depicted in Tables 1 and 2, generate five insertion mutants in which laminin P1 ligand is inserted directly following R in SEQ ID NO:4 (I-447), directly following FF in SEQ ID NO:5 (I-534), directly following T in SEQ ID NO: 6 (I-573), directly following N in SEQ ID NO:7 (I-587) and directly following T in SEQ ID NO:8 (I-713). No further experiments were demonstrated with I-713 other than to determine its packaging efficiency. The specification teaches that two of the insertions I-447 and I-587 can form particles but the ability of I-534 and I-573 to form particles is two orders of magnitude less (table 2). P1 interacts with integrin receptor. To analyze the infectivity of the AAV2 particles resulting from the four mutations, B16F10 and RN22 cells expressing P1 specific integrin on their surface were infected with particles produced comprising the mutant structural proteins. No binding of wild type AAV2 and I-534 and I-573 to these cells were detected. While, I-447 and I-587 were able to bind to both cells, B16F10 cells transfected with I-447 were as inefficient as wild-type cells in generating titer (table 3). Therefore, one viral particle that results from insertion of P1 into amino acid 587 (I-587) is shown to have increased infectivity of B16F10 cells. This mutant is at site 587 of AAV2 VP3. The specification also teaches at page 28 that VP3 protein was mutated by the insertion of Z34C domain of protein A but no indication about the ability of the structural protein to form particles or increase infectivity is provided. Post filing art by Reid et al (J. Virol.

76:4559-4566, 2002, referenced in applicants' arguments filed 11/22/04) demonstrate that this insertion is, like that in the instant specification, following amino acid 587 of VP3.

4) **State of Art**. AAV-2 can infect a wide variety of cell types according to Ruffing et al (page 3385, col 2, paragraph 2; applicant provided in the amendment filed 11/22/04) hence the vector has been considered a valuable tool for gene therapy for the delivery of therapeutic molecules. Mutational analysis of the AAV2 capsid proteins has been undertake to identify locations that will alter the tropism of AAV2 and hence "increase the infectivity". Despite numerous attempts to find locations that are tolerant of insertion and lead to an increase in infection, functionally relevant regions of AAV-2 did not always translate into actual sites for insertion. Buning et al (Gene Therapy, 2003, Vol 10, pages 1142-1151) review the art of targeting AAV-2 by insertion mutagenesis. According to Buning et al on page 1148, several parameters lead to the unpredictability of insertional mutagenesis (1) "surface display of a ligand alone is a prerequisite but not sufficient for a ligand-dependent infection by the virus mutant" (2) "scaffold sequences flanking the heterologous ligand are important for epitope display, (3) "Not every ligand, even if comparable in length, is tolerated at a specific insertion site" (page 1148, col 1, (2)). Therefore, using surface locations as determination of sites for insertion of any amino acid is a highly unpredictable art. Accordingly, it is demonstrated by Buning et al that I-587 alone presents promise for receptor specific peptides (see page 1143, col 2, paragraph 2). Hence using the corresponding method of the instant invention, a single species of insertion sites has reproducibly been demonstrated.

Wu et al (JVI, 2000, Vol 74, pages 8635-8647, applicant provided in the amendment filed 11/22/04) undertook a more systemic approach to characterize the capsid protein. Wu et al

teaches that the art of generating AAV2 structural proteins with mutations that exhibit increased infectivity and form particles with altered tropism is unpredictable. Wu generated 93 insertion mutants at 59 locations. Wu et al generated a functional map of the AAV2 capsid and demonstrated which sites could actually tolerate substitutions, deletions or insertions. The sites were mutated by insertion of epitopes or ligands, by alanine-scanning mutagenesis in which 2-5 amino acids are altered to alanine residues and epitope substitution mutations. In fact, Wu found that not all substitutions or insertions were the same and that regions that could tolerate alanine substitutions could not tolerate other types of substitutions and the ability to introduce FLAG into the capsid reduced or abolished particle formation (see Wu et al, page 8640, col 1-2 and table 4). Therefore, Wu et al inserted HA into loop structures, reasoning that insertion would not affect capsid assembly or stability. While 6 sites tolerated substitution, only two demonstrated altered tropism confirming that the state of the art of determining insertions sites based upon structural characteristics is highly unpredictable.

5) **Unpredictability of the art**. The instant specification teaches methods of identifying surface located regions of the structural proteins for the purpose of generating AAV particles that have increased infectivity. The specification teaches that sites useful for mutation can be identified by comparison of sequences of several AAV serotypes or by computer-assisted comparison of CPV, AAV2 and B19. Applicants then propose that utilization of these surface locations for insertional mutational would allow generation of particles that have an increase in infectivity. Applicants conclude "it is also possible likewise to introduce an insertion in to the five directly adjacent AAs located next to the bold AA, because these are likewise located within a loop in the AAV2 capsid" (page 16, line 25-28). However, applicants only demonstrate the

operability of a single insertion site with a single type of amino acid insertion, a P1 ligand, that leads to increased infectivity of P1 receptor containing cells thus altering the tropism of this vector. Given the broad nature of the recited structural proteins and the unknown nature of the amino acid insertion and the unknown numbers of insertions, the invention has a high level of unpredictability. The MPEP teaches, "However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. Atlas Powder Co. v. E.I. duPont de Nemours & Co., 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984); In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). (see MPEP 2164.08(b). As taught by Buning et al, it is highly unpredictable that demonstration of a surface loop will itself provide the functional characteristics for altered tropism or increased infectivity. Furthermore, the demonstration that P1 functions at I-587 to increase infectivity to B16F10 does not provide adequate teachings that any ligand in any site will also provide the recited functional characteristics. Finally, the ability to determine *a priori* the functional aspects of a protein based upon primary amino acid sequence is poorly established in the art. For example, Tseng and Liang teach that protein surfaces in particle experience very different selective pressure than other functional domains and global protein sequence and structure similarity are often unreliable for function prediction (see Introduction). Smith and Zhang provide teachings that confirm that inconsistencies and outright errors are encountered when assigning probable function to sequences (see page 1222, col 2, paragraph 1).

6) **Summary**. First, it would require undue experimentation to determine which of the structural proteins would result in an increase in infectivity of AAV and is capable of particle formation with altered tropism. Applicants do not disclose any other use for the mutated structural proteins then for use in generating AAV particles with increased infectivity. Secondly, applicants do not teach how to use those mutated structural proteins that cannot be used in an AAV to generate a particle with increased infectivity and it would require undue experimentation to determine an enabled use for this protein.

In view of predictability of the art to which the invention pertains and the lack of guidance in the specification: undue experimentation would be required to practice the claimed methods with reasonable expectation of success, absent a specific and detailed description in the specification. Given the above analysis of the factors which the courts have determined are critical in determining whether a claimed invention is enabled, it must be concluded that the skilled artisan would have had to have conducted undue unpredictable experimentation in order to practice the claimed invention.

Response to Arguments-35 USC § 112, 1st paragraph-written description and lack of enablement

Applicants traverse the rejections under 35 U.S.C 112, first paragraph on pages 7-8 of the amendment filed 10/2/06. Applicants argue that the new claims are free of the 112 first paragraph rejections as they do not require particle formation or increased infectivity.

Applicant's arguments filed 10/2/06 have been fully considered but they are not persuasive. Upon reconsideration, claims 41 and 42 have been rejected under 35 USC 112, first

paragraph for lack of written description and lack of enablement. These claims are drawn to methods of making and methods of using mutated structural proteins that do require that the proteins be part of an AAV particle with increased infectivity. While new claims 44, 46-48, 50 and 51 do not require particle formation, the claims are not supported by an enabled use for the recited particles.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101, which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 31, 32, 35-40, 42 and 44-50 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 121, 122, 130 and 143 of copending Application No. 10/498,163. **This rejection is maintained for**

reasons of record in the office action mailed 12/6/05 and 7/10/06 and restated below. The rejection has been extended to newly added claims 44-50.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claims because the examined claim is either anticipated by, or would have been obvious over, the reference claims. Although the conflicting claims are not identical, they are not patentably distinct from each other because the cited claims of the instant invention are generic to all that is recited in claims 121, 122, 130 and 143 of U.S. application 10/498,163. That is, the cited claims of U.S. application 10/498,163 anticipate and fall entirely within the scope of the rejected claims of the instant application. Specifically, the instant claims and U.S. 10/498,163 claims recite a structural (cap or capsid) protein and the nucleic acid coding for the structural protein with an insertion after an amino acid such as 587 (amino acid N in SEQ ID NO:7 of the instant claims). Claim 121 of US application 10/498,691 specifically recites insertion of RGD, which is a ligand that interacts with cell surface integrin receptors and is specifically designed to increase infectivity to cells as recited in claim 1 of the instant invention. The specification of 10/498,163 teaches that the amino acid 587 recited in claim 122 is specifically from AAV2 and corresponds to N of SEQ ID NO:7 of instant claim 1. The capsid proteins VP1, VP2 and VP3 are components of AAV particles and are all encoded by the same transcript and result from alternative splicing. Instant application 10/498,163 refers to the amino acids as numbered from the N-terminus of VP-1. However, the insertion if after amino acid 587 could be in VP-3 as recited in claim 29 and 30 of the instant invention as the amino acid recited

as 587 is included in VP-1, VP2 and VP-3. An insertion of an RGD ligand at 587 alters binding at the heparan sulfate receptor as taught by 10/498,163.

Additionally, if a patent resulting from the instant claims was issued and transferred to an assignee different from the assignee holding the Application No. 10/498,163, then two different assignees would hold a patent to the claimed invention of Application No. 10/498,163, and thus improperly there would be possible harassment by multiple assignees.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Response to Argument

Applicants' request that the response to this rejection be deferred until allowable subject matter has been identified is acknowledged. However, the rejection is maintained until the recited claims are patented or a terminal disclaimer is filed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Maria B. Marvich, PhD whose telephone number is (571)-272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Maria B Marvich, PhD
Examiner
Art Unit 1633